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EDUCATIONAL ARTICLE

New Antiplatelet Strategies in Atherothrombosis and Their Indications

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Antiplatelet agents (APA) are used to reduce the risk of major cardiovascular events in various settings. When used for secondary prevention, antiplatelet monotherapy is associated with a relative risk reduction of such ischemic events of 25% compared to a placebo. New strategies are based on dual APA therapy. Aspirin-clopidogrel combination therapy is effective in situations of acute vessel injury such as myocardial infarction, coronary stenting and, possibly, peripheral stenting. GPIIb/IIIa inhibitors and loading doses of clopidogrel also have a place in these acute settings. In contrast, the aspirin-clopidogrel combination has proven disappointing in stable patients with cardiovascular disease, with no beneficial effect and, often, more bleeding events. Combination therapy with aspirin and extended-release dipyridamole may be more beneficial than very low doses of aspirin in ischemic stroke, but its use is limited by adverse effects. Overall, aspirin remains the first-line monotherapy of choice for patients with atherothrombosis, while clopidogrel is a valuable alternative. New antiplatelet strategies are in the pipeline, and clinically relevant laboratory tests of APA response may soon help to tailor treatment.

Keywords: Aspirin; Clopidogrel; Antiplatelet agents; Atherothrombosis.

Introduction

Platelets contribute to the initiation and aggravation of atherosclerosis in humans and in animal models. Major steps in arterial thrombosis include platelet activation and aggregation, both following contact with subendothelial structures and via thrombin generation.¹ Antiplatelet agents (APA) are therefore key tools in the treatment of atherothrombosis. In addition to their well-established role in thrombus formation, there is growing evidence that platelets are also involved in the progression of atherosclerotic lesions. When activated, platelets release granules containing cytokines and growth factors that, together with thrombin, contribute to the migration and proliferation of smooth-muscle cells and monocytes.² Thus, in

addition to their preventive role in acute thrombosis, APA can also inhibit the platelet contribution to lesion progression.^{3,4}

There are currently four major classes of antiplatelet drugs. Aspirin, thienopyridines (ticlopidine and clopidogrel) and phosphodiesterase (PDE) inhibitors (dipyridamole and cilostazol) are platelet function inhibitors, while the glycoprotein (GP) IIb/IIIa antagonists specifically prevents aggregation by inhibiting the fibrinogen receptor $\alpha_{IIb}\beta_3$.

For several years a one-drug-fits-all policy governed the secondary prevention of ischemic events in cardiovascular patients. Aspirin was most often prescribed. Recently, several trials have tested the efficacy and safety of new APA strategies, mostly APA combinations, in secondary prevention – the subject of this review.

Role of Platelets in Atherothrombosis

Platelet activation involves several mechanisms. After atherosclerotic plaque rupture, platelet adherence to subendothelial components like collagen triggers

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numerous amplification pathways required for the formation of a stable thrombus. Soluble agonists like thromboxane A₂ (TxA₂) and adenosine diphosphate (ADP) are the main amplifiers of platelet activation (Fig. 1). Following platelet activation the GPIIb/IIIa receptor undergoes a conformational change that allows activated platelets to stick together via bridges formed by the GPIIb/IIIa complex and proteins such as fibrinogen, fibrin, and von Willebrand factor. Activated platelets also stimulate the coagulation cascade and accelerate thrombin formation, further contributing to thrombus growth.

Aspirin

The antiplatelet effect of aspirin is mainly due to irreversible inhibition of cyclooxygenase (COX)-1 activity, which normally catalyzes the conversion of arachidonic acid to prostaglandin (PG) H₂. PGH₂ is a precursor of several bioactive prostanoids, including TxA₂.⁵ Although aspirin has a short half-life (15 to 20 min) in the human circulation, it induces a rapid and permanent defect in TxA₂-dependent platelet function. As only 10% of the platelet pool is replenished each day, a single daily dose of aspirin is sufficient to maintain virtually complete inhibition of platelet TxA₂ production.⁶

The ISIS-2 study represented an important milestone, by showing that aspirin reduced mortality after a myocardial infarction (MI) as effectively as streptokinase.⁷ Several other trials followed, and

a meta-analysis showed a 25% relative reduction in the risk of vascular death, myocardial infarction and stroke with antiplatelet therapy (mostly aspirin) compared to a placebo in various categories of high-risk cardiovascular patients.⁸ In patients with acute myocardial infarction, the absolute reduction in risk was 3.8% at 1 month and the “number needed to treat” (NNT) for one month to avoid one major vascular event was 26. Current evidence suggests that a daily aspirin dose of 75–160 mg is optimal for long-term prevention in high-risk patients, together with a loading dose of 325 mg when an immediate antithrombotic effect is required (Table 1).^{9,10}

The benefit of aspirin on coronary heart disease and stroke has been extensively studied, whereas fewer data are available on peripheral arterial disease (PAD). PAD is often associated with atherosclerosis in other vascular territories, and patients with this disorder are at markedly elevated risk of vascular events and death.¹¹ However, among 9214 patients with PAD included in the Antithrombotic Trialists’ Collaboration Study, the 22% reduction in ischemic events referred to other APA than aspirin in 60% of cases. Nevertheless, the benefit of aspirin on cardiovascular events has been firmly demonstrated in a number of other high-risk settings,¹² and PAD patients are clearly a high-risk population.¹³

Aspirin is the antiplatelet drug recommended for PAD in the American College of Cardiology / American Heart Association guidelines¹⁴ (level of evidence: A). The Inter-Society Consensus for the Management of

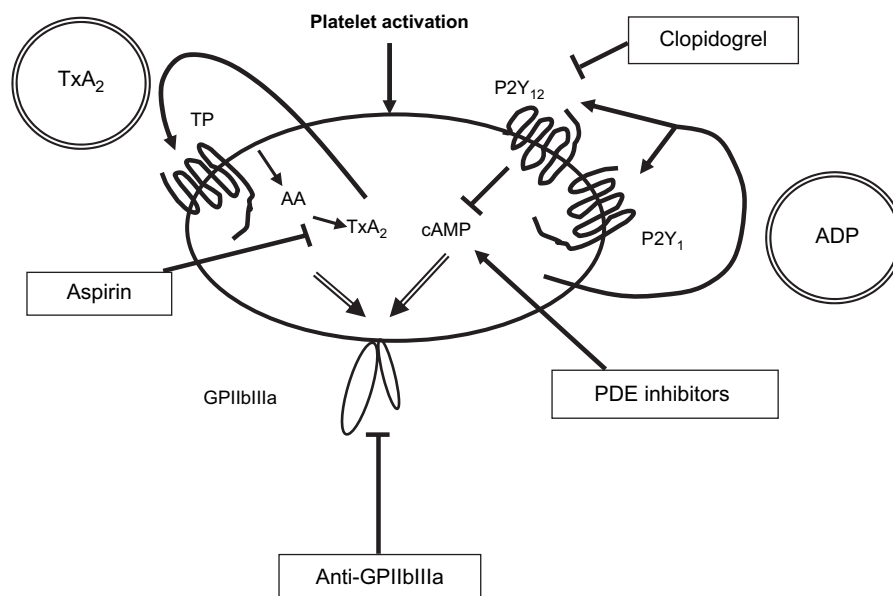


Fig. 1. Main amplification pathways of platelet activation and action of antiplatelet agents (APA). The two main amplification pathways are the thromboxane A₂ (TxA₂) and adenosine diphosphate (ADP) pathways, which are targeted by the most widely used APAs. AA: arachidonic acid, cAMP: cyclic adenosine monophosphate, PDE: phosphodiesterases.

Table 1. Antiplatelet treatments and their indications.^{9,10,14,15,54–58}
Recent studies have not added significant modifications

Clinical condition	Current indications from consensus statements
Ischemic heart disease	
Acute coronary artery injury (MI, stenting)	
Dual aspirin-clopidogrel treatment	Yes – 1 to 12 months
Clopidogrel loading dose	Yes – 300 to 600 mg
GPIIb IIIa inhibitors	Yes
Stable IHD	
Aspirin	Yes – 75 to 325 mg/d
Clopidogrel	Yes – 75 mg/d
Dual aspirin-clopidogrel treatment	No
Ischemic cerebral disease	
Acute stroke	
Aspirin	Yes 160–300 mg
Clopidogrel	No
Dual aspirin-clopidogrel treatment	No
Dual aspirin-dipyridamole treatment	No
Stable disease	
Aspirin	Yes – 75 to 325 mg/d
Clopidogrel	Yes – 75 mg/d
Dual aspirin-clopidogrel treatment	No
Dual aspirin-dipyridamole treatment	Yes
Peripheral arterial disease	
Acute vessel injury (stenting)	
Dual aspirin-clopidogrel treatment	Yes
Stable PAD	
Aspirin	Yes – 75 to 325 mg/d
Clopidogrel	Yes – 75 mg/d
Dual aspirin-clopidogrel treatment	No

Peripheral Arterial Disease (TASC II)¹⁵ is more circum-spect, with a grade-C level of evidence, probably because of the lack of powered placebo-controlled trials in this setting,¹⁶ which is unlikely to be run owing to ethical issues.

The Drug Evaluation in Atherosclerotic Vascular Disease in Diabetes (DAVID) study¹⁷ showed a 45% reduction in all-cause mortality among patients with PAD and diabetes treated with picotamide (a combined inhibitor of T×A2 synthase and receptor) compared with aspirin. However, these promising data need to be confirmed in a larger population before picotamide can be considered as a replacement for aspirin in patients with PAD.

Thienopyridines

Thienopyridines are prodrugs that need to be activated by liver cytochrome P450 isoenzymes and can therefore only be taken orally.¹⁸ The active metabolite selectively targets P2Y₁₂,¹⁹ one of the two ADP receptors on the platelet surface, and irreversibly binds two

cysteine residues. The thienopyridines induce permanent platelet hypo-responsiveness to ADP.

Ticlopidine was the first thienopyridine to arrive on the market, but the risk of neutropenia (in about 1% of patients) and thrombotic thrombocytopenic purpura (0.02%) limited its use. Clopidogrel, with lower side effects, has now largely supplanted ticlopidine.

As thienopyridines have to be metabolized before becoming active, there is a time lag before their anti-platelet action occurs. Inhibition of ADP-induced platelet aggregation reaches its plateau after 5 days of standard-dose therapy (500 mg/d ticlopidine or 75 mg/d clopidogrel).²⁰ After acute vessel injury, such as following coronary stenting, the onset of clopidogrel action can be brought forward to between 2 and 5 hours by giving a loading dose.²¹ Two prospective studies showed that a 600-mg loading dose of clopidogrel before PCI for elective indications or for non ST-elevation myocardial infarction was safe and more effective than the standard 300-mg dose on recurrent ischemic events.^{22,23} Finally, the ALBION study (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) suggested an incremental benefit of a 900-mg loading dose.²⁴

The CAPRIE study evaluated the efficacy and safety of clopidogrel compared to aspirin for secondary prevention in 19185 cardiovascular patients.²⁵ It showed a relative reduction in the risk of myocardial infarction, ischemic stroke and vascular death of 8.7% ($p = 0.04$), after a mean follow-up of 1.9 years, and an absolute risk reduction of 0.51% per year (NNT = 196 to avoid one ischemic event). Subgroup analyses suggested that the clinical benefit was greater in PAD patients²⁵ and other high-risk patients.²⁶ However, it should be noted that many hypotheses raised by subgroup analyses were subsequently refuted in trials specifically designed to test them,²⁷ and that prospective studies are still needed to identify patients with stable vascular disease who might benefit more from clopidogrel than from aspirin.

Thienopyridines and aspirin act on the two main physiological platelet amplification pathways (the ADP and T×A₂ pathways, respectively), therefore their combination might be beneficial for patients with a high risk of vascular occlusion. This issue was evaluated in acute coronary injury and stable cardiovascular diseases.

Dual clopidogrel and aspirin therapy in acute coronary injury

The CURE study (Clopidogrel in Unstable angina to prevent Recurrent Events) showed that clopidogrel,

given to patients with unstable angina or acute MI without ST elevation, yielded a 2.1% absolute reduction (NNT = 48, $p < 0.0001$) in the risk of major ischemic events.²⁸ Recent studies include the CLARITY-TIMI 28 trial (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis In Myocardial Infarction) which demonstrated the benefit of clopidogrel, given in addition to fibrinolytic therapy and aspirin, in patients presenting within 12 hours after the onset of MI with ST elevation.²⁹ Clopidogrel addition to the standard therapy yielded a relative reduction of 37% (95% CI [24–47], $p < 0.001$) and an absolute reduction of 6.7% (NNT = 15) in the frequency of a composite endpoint (occluded infarct-related artery on angiography, or death or recurrent myocardial infarction before angiography). This effect was maintained at 1 month, with an absolute reduction of 2.5% ($p = 0.03$) in a composite clinical endpoint consisting of major ischemic events. These results are in line with those of the CLOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT),³⁰ in which 45852 patients admitted for suspected acute MI were randomly allocated either to clopidogrel 75 mg daily ($n = 22\,961$), without a loading dose, or to a matching placebo ($n = 22\,891$), in addition to aspirin 162 mg daily. Allocation to clopidogrel was associated with an absolute reduction of 0.9% (NNT = 111, $p = 0.002$) in the risk of death, reinfarction or stroke.

Aspirin-thienopyridine combination therapy is now the standard preventive treatment after percutaneous coronary intervention (PCI) with stent implantation, as it is superior to anticoagulation^{31,32} and to aspirin alone.^{33,34} The recommended duration of aspirin-clopidogrel combination therapy after acute coronary artery injury ranges from 1 to 12 months (Table 1) and is controversial, particularly in view of late thrombosis after APA withdrawal in patients with drug-eluting stents (DES).³⁵ By analogy with PCI, thienopyridines and aspirin are also combined after stent implantation in the renal and lower-limb arteries, even though there are no consistent data supporting this strategy. The results of ongoing trials in this indication are eagerly awaited, including those of the CAMPER study (Effect of Clopidogrel vs. Placebo, on a Background of Standard Care including Aspirin, in Maintaining the Patency of Lower Limb Arteries After Angioplasty).

Dual clopidogrel and aspirin therapy in stable cardiovascular diseases

Contrary to situations of acute coronary artery injury, aspirin-thienopyridine combination therapy has been so far disappointing in other clinical settings.

In ischemic cerebrovascular disease (ICD), The MATCH trial (Management of Atherothrombosis With Clopidogrel in High-Risk Patients) randomised 7599 patients with a recent transient ischemic attack (TIA) or ischemic stroke to either clopidogrel plus aspirin (both 75 mg daily) or clopidogrel plus placebo during 18 months.³⁶ The dual APA strategy did not show any supplementary reduction in the composite endpoint of ischemic stroke, myocardial infarction, vascular death, or readmission for acute ischemia, and was associated with an increase in hemorrhagic complications (1.9%, vs 0.6% $P < 0.001$). The design of the study also raised several concerns, including the absence of an aspirin arm, despite the lack of proven efficacy of clopidogrel compared to aspirin in these acute (<7 days) neurovascular patients.³⁷ The high percentage (53%) of infarcts related to small-vessel disease is a matter of concern, as the pathophysiology of arterial occlusion may be different in small-vessel disease compared to typical atherothrombotic vascular lesions.³⁸

The CHARISMA study (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) was designed to test the hypothesis that “long-term treatment with a combination of clopidogrel plus aspirin might provide greater protection against cardiovascular events than aspirin alone in a broad population of patients at high risk”.³⁹ This trial enrolled over 15000 patients, who were randomized and followed for a median of 28 months. The primary combined endpoint myocardial infarction, stroke, and death from cardiovascular causes was reached by 6.8% of patients allocated to clopidogrel plus aspirin and by 7.3% of the patients allocated to placebo plus aspirin ($P = 0.22$). The respective rates of severe bleeding were 1.7% and 1.3% ($P = 0.09$). The risk of moderate bleeding showed a relative increase of 62% (95% CI [27–110], $p < 0.001$) in the clopidogrel–aspirin group. The analysis of pre-defined subgroups suggested that patients defined as “symptomatic” (with major cardiovascular events) drew more benefit of the dual therapy than “asymptomatic” (with multiple risk factors) patients, with a marginally significant absolute reduction of 1% ($p = 0.046$). As stated above, subgroup analyses should be interpreted with caution, especially as some of the “asymptomatic” patients had major cardiovascular events and as “symptomatic” patients probably had multiple risk factors.⁴⁰ These results should be considered as hypothesis generating and need to be confirmed with trials in specific populations (i.e. coronary artery disease, cerebral artery disease, PAD and patients with symptomatic aortic atheroma.)

Finally, dual therapy is being tested in a surgical setting in the CASPAR study (Clopidogrel and Acetylsalicylic acid in bypass Surgery for Peripheral ARterial disease). This trial is evaluating whether clopidogrel versus placebo (on a background of aspirin 75–100 mg/d) will increase the rate of primary patency, limb salvage and survival in patients receiving a below-knee bypass graft for PAD. This study was recently completed and the results should be presented in March 2007 at the American College of Cardiology meeting.

Altogether, available evidence suggests a beneficial effect of dual APA therapy based on aspirin and clopidogrel in patients with acute coronary artery injury but not in patients with stable cardiovascular disease. However, the risk of bleeding is sometimes increased by this dual APA therapy.

Phosphodiesterase Inhibitors

PDEs are a family of nine enzymes catalyzing the hydrolysis of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP). Dipyridamole and cilostazol act as PDE inhibitors, raising platelet levels of cyclic adenosine monophosphate and thereby inhibiting platelet function.⁴¹ Dipyridamole also enhances the release and prevents the degradation of endothelial prostaglandin PGI₂, a potent inhibitor of platelet aggregation. These drugs also have vasodilator activity mediated by an action on the endothelium.⁴¹ Finally, cilostazol inhibits the proliferation of vascular smooth muscle cells.⁴¹

Although the clinical benefit of dipyridamole in the prevention of cardiovascular events in coronary patients is disappointing,⁴² with potential adverse hemodynamic effect,⁴³ PDE inhibitors have recently been a focus of attention in the treatment of patients with cerebrovascular disease and those with bare-metal stents (BMS).^{44,45}

Dual antiplatelet therapy with aspirin and dipyridamole was evaluated in cerebrovascular disease patients in the European Stroke Prevention Study (ESPS-2), the results of which were recently confirmed by the ESPRIT trial.⁴⁴ This latter study, a randomized open-label trial, evaluated the efficacy of aspirin along and combined with dipyridamole in 2739 patients with mildly disabling cerebrovascular disease, over a mean follow-up of 3.5 years. Meta-analysis of the two studies showed an absolute reduction of 2.9% (NNT=35) in the endpoint combining vascular death, non fatal stroke and myocardial infarction in the group of patients treated with aspirin and dipyridamole compared to patients treated with aspirin

alone. However, 34% of the patients discontinued the dual therapy because of adverse effects (mainly headache) compared to 16% of the patients in the aspirin-alone arm. One limitation of the ESPRIT study is that 44% of the patients in each arm received only 30 mg of aspirin per day, a dose that is not recommended for secondary prevention. Some of the results are surprising: the supplementary benefit of aspirin-dipyridamole over aspirin alone was larger in the intention-to-treat analysis than in the on-treatment analysis and there were significantly fewer major bleeding events in the combination therapy arm.

The 15500-patient PRoFESS study (the Prevention Regimen for Effectively Avoiding Second Strokes), with results expected in 2008, is comparing directly aspirin plus dipyridamole with clopidogrel monotherapy for the prevention of recurrent stroke and should provide statistically robust estimates of comparative efficacy.

Recently cilostazol, having antiproliferative properties, was evaluated as a systemic therapy for the prevention of restenosis after BMS implantation, in the Cilostazol for Restenosis Trial (CREST).⁴⁵ In this randomized, double-blind, placebo-controlled trial, 705 patients were allocated to either cilostazol (50 mg bid) or placebo for 6 months. At 6 months, the intrastent late luminal loss was slightly but significantly lower in the cilostazol-treated group than in the placebo group (0.91 ± 0.60 vs 1.06 ± 0.69 , $P = 0.01$). There was no difference in the rate of clinical events, and particularly no excess of bleeding in the cilostazol group. Owing to its anti-PDE III properties, cilostazol is contraindicated in patients with severe congestive heart failure. Indeed, the CREST study excluded patients with a left ventricular ejection fraction below 30%. The FDA contraindicates cilostazol in patients with congestive heart failure of any severity (available on January 14, 2007 at http://www.fda.gov/cder/news/cilostazol/cilo_label.htm), and this drug is not currently available in all European countries.

Overall, cilostazol is not recommended for the prevention of cardiovascular events and its use is currently limited to the relief of symptoms of claudication in PAD patients.⁴⁶

GPIIb/IIIa Antagonists

There are currently three classes of GPIIb/IIIa antagonist: abciximab, a Fab fragment of a humanized murine monoclonal antibody; eptifibatide, a synthetic cyclic heptapeptide; and tirofiban, a non-peptide antagonist of GPIIb/IIIa. All preparations are administered intravenously. Oral preparations failed to

provide long-term prevention of recurrent ischemic events and were associated with an increase in the rates of all-cause mortality and bleeding complications,⁴⁷ possibly due to incomplete blockade of GPIIb/IIIa. Intravenous GPIIb/IIIa antagonists are indicated in acute clinical situations and their efficacy is well documented in the acute coronary syndrome. The Intracoronary Stenting and Antithrombotic Regimen Rapid Early Action for Coronary Treatment 2 trial of abciximab (ISAR-REACT 2) showed a 25% reduction (relative risk 0.75; 95% CI [0.58–0.97]; $P=0.03$) in the risk of a composite endpoint (death, myocardial infarction, or urgent target vessel revascularization) in patients with non-ST-segment elevation acute coronary syndrome undergoing angioplasty after pretreatment with 600 mg of clopidogrel.⁴⁸ Abciximab is also being studied in the treatment of acute cerebrovascular disease, with promising results.⁴⁹ Current data do not support the use of GPIIb/IIIa inhibitors in patients with acute cerebrovascular disease,⁵⁰ bleeding risk being a major concern in these patients but large prospective trials are warranted.

Conclusion

APAs are important agents in the medical management of atherothrombosis. Platelets have several amplification pathways, and each APA only partially impairs their function. The combination of aspirin and clopidogrel shows promise in the treatment of patients at a high risk of vascular occlusion, but it is currently only recommended in situations of acute coronary artery injury, such as acute coronary syndrome and stent implantation, whereas the results of trials in patients with stable cardiovascular disease favour monotherapy. The combination of aspirin with dipyridamole may be beneficial in cerebrovascular disease patients, but its use is restricted by adverse side-effects.

New and possibly more potent molecules targeting the well-characterized ADP and $T \times A_2$ platelet amplification pathways are under study (Prasugrel⁵¹ and S18886⁵² for example). There are also many other amplification and regulatory mechanisms⁵³ that are not directly targeted by current APA and might offer new drug targets. A closer perspective is the development of clinically relevant biological tests to determine APA response. This may soon help tailor APA therapy and improve the individual risk-benefit ratio.

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Take-home message

- When a single anti-platelet agent is needed, aspirin remains the first-line treatment of choice for patients with atherothrombosis. Clopidogrel is a valuable alternative.
- The combination of aspirin and a thienopyridine (eg clopidogrel) should currently be restricted to situations of acute coronary artery injury (including stent implantation).
- New antiplatelet drugs are in the pipeline, as well as clinically relevant biological tests for anti-platelet response that may help tailor treatment.

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